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WASHINGTON
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PARIS

DEC 17 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

SUITABILITY PETITION

This petition is submitted pursuant to 21 CFR parts 10.20 and 10.30, as provided for in 21 CFR 314.93 and Section 505(j)(2)(c) of the Federal Food, Drug and Cosmetic Act to request the Commissioner of the Food and Drug Administration to declare that the drug product Cephalexin Dispersible Tablets 125 mg, 250 mg and 500 mg are suitable for submission as an abbreviated new drug application (ANDA).

A. Action Requested

The petition is submitted for a change in dosage form of the drug product from "powder for oral suspension" and "capsules" to "dispersible tablets". The listed drug product is Keflex® for oral suspension 125 mg/5 mL and 250mg/5 mL, and Keflex® Pulvules 250 mg and 500 mg manufactured by Eli Lilly and Company (Lilly). Cephalexin will be marketed as dispersible tablets in dosage strengths of 125 mg, 250 mg and 500 mg. The drug, the route of administration and the recommendations for use are the same as the listed drug product. The proposed product would differ only in dosage form from Lilly's marketed product.

The proposed drug product is expected to demonstrate bioequivalence to both 250 mg/5 mL suspension and 500 mg capsule dosage forms of the listed product which will be submitted at a later date.

B. Statement of Grounds

Dispersible tablet is presented for administration by dispersing a single tablet in a specified amount of water.

The new dosage form would be a better alternative to the powder for oral suspension with regards to the following advantages:

Unit dose dispensing.
Convenience to the patient with respect to the administration during traveling.
Storage of the product will not require special condition like refrigeration.

99P-5451

CP 1

Better precision of dosage over the traditional teaspoonful.
Ease of carrying.

Additionally, 250 mg and 500 mg dispersible tablets can be a viable alternative to the capsule dosage form for geriatric patients who have problems swallowing the solid oral dosage forms.

As the proposed product 'will differ only in dosage form, and the indications, strength, route of administration, intended patient population and recommendations for use remain the same as Lilly's marketed product, therefore there will be no difference in the safety and efficacy of the proposed dispersible tablets.

A package insert of Lilly's Keflex® is attached along with the draft package insert of the proposed Cephalexin Dispersible Tablets.

C. **Pediatric Use Information**

As the package insert of Lilly's Keflex® for oral suspension contains adequate dosing and administration information for the pediatric population, no additional studies are required.

D. **Environmental Impact**

An environmental assessment report on the action requested in this petition is not required under 21 CFR 25.24.

E. **Economic Impact**

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the Agency.

F. **Certification**

The undersigned certifies that to the best of its knowledge, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Sincerely,

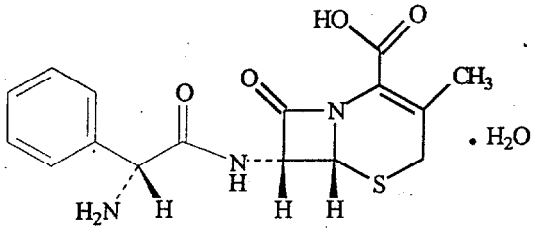
Nicholas M. Fleischer, R.Ph., Ph.D.
Director of Biopharmaceutics
THE WEINBERG GROUP INC.

CEPHALEXIN DISPERSIBLE TABLETS
Rx only

DESCRIPTION

Cephalexin, USP is a semisynthetic cephalosporin antibiotic intended for oral administration. It is 7-(D-α-amino-α-phenyl-acetamido)-3-methyl-3-cephem-4-carboxylic acid monohydrate. cephalexin has the molecular formula $C_{16}H_{17}N_3O_4S \cdot H_2O$ and the molecular weight is 365.4.

Cephalexin has the following structural formula:



The nucleus of cephalexin is related to that of other cephalosporin antibiotics.-The compound is a zwitterion; i.e., the molecule contains both a basic'and an acidic group. The isoelectric point of cephalexin in water is approximately 4.5 to 5.

The crystalline form of. .cephalexin which is available is a monohydrate. It is a white crystalline solid having a bitter taste. Solubility in water is low at room temperature; 1 or 2 mg/ml may be dissolved readily, but higher concentrations are obtained with increasing difficulty.

The cephalosporins differ from penicillins in the structure of the bicyclic ring system. Cephalexin has a *D*-phenylglycyl group as substituent at the 7-amino position and an unsubstituted methyl group at the 3-position.

Each dispersible tablet for oral administration contains cephalexin monohydrate equivalent to 125 mg, 250 mg or 500 mg of cephalexin.

The inactive ingredients will be furnished when ANDA is submitted, since this is' proprietary information, The inactives are GRAS ingredients at the appropriate levels.

CLINICAL PHARMACOLOGY

Human Pharmacology - Cephalexin is, acid stable and may be given without regard to meals. It is rapidly absorbed after oral administration. Following doses of 250 mg, 500 mg, and lg, average peak serum levels of approximately 9, 18, and 32 mcg/mL respectively were obtained at 1 hour. Measurable levels were present 6 hours after administration. Cephalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies showed that over 90% of the drug was excreted unchanged in the urine within S hours. During this period, peak urine concentrations following the 250 mg, 500 mg, and 1g doses were approximately 1,000, 2,200, and 5,000 mcg/mL respectively.

Microbiology - In vitro tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cephalexin has been shown to be active against most strains of the following microorganisms both ***in vitro*** and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobes, Gram-positive :

Staphylococcus aureus (including penicillinase-producing strains)
Staphylococcus epidermidis (penicillin-susceptible strains)
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobes. Gram-negative

Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Moraxella (Branhamella) catarrhalis
Proteus mirabilis

Note--Methicillin-resistant staphylococci and most strains of enterococci ***(Enterococcus faecalis*** [formerly ***Streptococcus faecalis***]) are resistant to cephalosporins, including cephalexin. It is not active against most strains of ***Enterobacter*** spp, *Morganella morganii*, and *Proteus vulgaris*. It has no activity against ***Pseudomonas*** spp or ***A cine tobacter calcoace ticus.***

Susceptibility Tests **- Diffusion Technique?** Quantitative methods that require measurement of done diameters provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure' that has been recommended for use with disks to test the susceptibility of microrganisms to cephalexin uses the 30 mcg cephalothin disk. Interpretation involves correlation of the diameter obtained in the disk test with the minimal inhibitory concentration (MIC) for cephalexin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 mcg cephalothin disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ ***18***	(S) Susceptible
15-17	(I) Intermediate
≤ ***14***	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate" indicates that the result should' be considered equivocal, and if microrganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in

interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrcobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections, (See CLINICAL PHARMACOLOGY section for . information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standardized susceptibility test procedures require the use of laboratory control microorganisms. The 30 mcg cephalothin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
E. coli ATCC 25922	15-21
S. aureus ATCC 25923	**29-37**

Dilution techniques: Quantitative methods that are used to determine MICs provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution method[2] (broth, agar, microdilution) or equivalent with cephalothin powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
< 8	(S) Susceptible
-16	(I) Intermediate
≥ **32**	(R) Resistant

Interpretation should be as stated above for results using diffusion techniques.

As with standard diffusion techniques, dilution methods require the use of laboratory control microrganisms. Standard cephalothin powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
E. coli ATCC 25922	**4-16**
S. aureus ATCC **292** 13	0.12-0.5

INDICATIONS AND USAGE

Cephalexin dispersible tablets are indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Respiratory tract infections caused by *S. pneumoniae* and *S. pyogenes* (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cephalexin is generally effective in the eradication of streptococci from the nasophatynx; however, substantial data establishing the efficacy of cephalexin in the subsequent prevention of rheumatic fever are not available at present.)

Otitis media due to *S. pneumoniae*, *H. influenzae*, staphylococci, streptococci and *M. catarrhalis*.

Skin and skin structure infections caused by staphylococci and/or streptococci
Bone infections caused by staphylococci and/or *P. mirabilis*
Genitourinary tract infections, including acute prostatitis caused by *E. coli*, *-P. mirabilis*, and *K. pneumoniae*

Note - Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS

Cephalexin is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE CEPHALEXIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to cephalexin.

Pseudomembranous colitis has been reported with nearly all antibacteiral agents, including cephalexin, and may range from mild to life threatening. Therefore, it is important to consider this diagnosis in patients with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, considerations should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacteiral drug clinically effective against *Clostridium difficile* colitis.

Usage in Pregnancy - Safety of this product for use during pregnancy has not been established.

PRECAUTIONS

General -- Patients should be followed carefully so that any side effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to cephalexin occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or corticosteroids).

Prolonged use of cephalexin may result in the overgrowth. of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Cephalexin should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Indicated surgical procedures should be performed in conjuction with antibiotic therapy.

As a result of administration of cephalexin, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP.)

As with other ß-lactams, the renal excretion of cephalexin is inhibited by probenecid.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy-- Pregnancy Category B -- The daily oral administration of cephalexin to rats in doses of 250 or 500 mg/kg prior to and during pregnancy, or to rats and mice during the period of organogenesis only, had no adverse effect on fertility, fetal viability, fetal weight, or litter size. Note that the safety of cephalexin during pregnancy in humans has not been established.

Cephalexin showed no enhanced toxicity in weanling and newborn rats as compared with adult animals. Nevertheless, because the studies in humans cannot rule out the possibility of harm, cephalexin should be used during pregnancy only if clearly needed.

Nursing Mothers-- The excretion of cephalexin in the milk increased up to 4 hours after a 500 mg dose; the drug reached a maximum level of 4 mcg/mL, then decreased gradually and had disappeared 8 hours after administration. Caution should be exercised when cephalexin is administered to a nursing woman.

ADVERSE REACTIONS

Gastrointestinal --- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely. The most frequent side effect has been diarrhea. It was very rarely severe enough to warrant cessation of therapy. Dyspepsia, gastritis, and abdominal pain have also occurred. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hypersensitivity --- Allergic reactions in the form of rash, urticaria, angioedema, and, rarely, erythema multiforme, Stevens Johnson syndrome or toxic epidermal necrolysis have been observed. These reactions usually subsided upon discontinuation of the drug. In ***some*** of these reactions, supportive therapy may be necessary. Anaphylaxis has also been reported.

Other reactions have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, arthralgia, arthritis, and joint disorder. Reversible, interstitial nephritis has been reported rarely. Eosinophilia, neutropenia, thrombocytopenia, and slight elevations in AST (SGOT) and ALT (SGPT) have been reported.

OVERDOSAGE

Signs and Symptoms -- Symptoms of oral overdose may include nausea, vomiting, epigastric distress, diarrhea and hematuria. If other symptoms are present, it is probably secondary to an underlying disease state, an allergic reaction or toxicity due to ingestion of a second medication.

Treatment ---To obtain up-to-date information about the treatment of overdose, a good resource is **your** certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the ***Physicians' Desk Reference (PDR)***. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs and unusual drug kinetics in your patient.

Unless 5 to 10 times the normal dose of cephalexin has been ingested, gastrointestinal decontamination should not be necessary.

Protect **the** patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis. hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of cephalexin; however, it would be extremely unlikely that one of these procedures would be indicated.

The oral median lethal dose of cephalexin in rats is > 5,000 mg/kg.

DOSAGE AND ADMINISTRATION

Cephalexin dispersible tablets are administered orally.

Adults-- The adult dosage ranges from 1 to 4 g daily in divided doses. The usual adult dose is 250 mg every 6 hours. For the following infections, a dosage of 500 mg may be administered every 12 hours: streptococcal pharyngitis, skin and skin structure infections, and uncomplicated cystitis in patients over 15 years of age. Cystitis therapy should be continued for 7 to 14 days. For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of cephalexin greater than 4 g are required, parenteral cephalosporins, in appropriate doses, should be considered.

Pediatric Patients - The usual recommended daily dosage for pediatric patients is **25** to 50 mg/kg in divided doses. For streptococcal pharyngitis in patients over 1 year of age and for skin and skin structure infections, the total daily dose may be divided and administered every 12 hours.

Cephalexin Dispersible Tablets

Weight	125 mg Tablet
10 kg (22 lb)	1/2 to 1 tab q.i.d.
20 kg (44 lb)	1 to 2 tabs q.i.d.
40 kg (88 Ib)	2 to 4 tabs q.i.d.
Weight	250 mg Tablet
20 kg (44 Ib)	1/2 to 1 tab q.i.d.
40 kg (88 lb)	1 to 2 tabs q.i.d.

or

Weight	125 mg Tablet
10 kg (22 lb)	1 to 2 tabs b.i.d.
20 kg (44 lb)	2 to 4 tabs b.i.d.
40 kg (88 lb)	4 to 8 tabs b.i.d.
Weight	250 mg Tablet
10 kg (22 lb)	1/2 to 1 tab b.i.d.
20 kg (44 lb)	1 to 2 tabs b.i.d.
40 kg (88 lb)	2 to 4 tabs b.i.d.

In severe infections, the dosage may be doubled.

In the therapy of otitis media, clinical studies have shown that a dosage of 75 to 100 mg/kg/day in 4 divided doses is required.

In the treatment of ß-hemolytic streptococcal infections, a therapeutic dosage of cephalexin should be administered for at least 10 days.

Cephalexin Dispersible Tablets should be dispersed in one teaspoonful of water before administration

HOW SUPPLIED:

Cephalexin Dispersible Tablets, 125 mg, 250 mg and 500 mg.
Packaging size to be determined.

Store at a controlled room temperature, 15" to 30°C (59° to 86" F) protected from moisture.

Dispense in tight, light-resistant container.

REFERENCES

1. National Committee for Clinical Laboratory Standards: Performance standards for antimicrobial disk susceptibility tests - 5th ed. Approved Standard NCCLS Document M2-A5, Vol 13, No 24, NCCLS, Villanova, PA. 1993.

2. National Committee for Clinical Laboratory Standards: Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically -3rd ed. Approved Standard NCCLS Document M7-A3, Vol 13, No 25, NCCLS, Villanova, PA. 1993.

November 1999

HOW SUPPLIED

ILOTYCIN® (Erythromycin Ophthalmic Ointment, USP, 0.5%) No. 52 is available in the following sizes:
1/8 oz. (3.5 g) tamper-resistant tube—(NDC 0777-1863-17-Prod. No. FL09234

DO NOT USE IF BOTTOM RIDGE OF TUBE CAP IS EXPOSED.

1 g plastic container (in cartons of 50)—(NDC 0777-1863-52)-Prod. No. FL09232

DO NOT USE IF CLICK IS NOT HEARD AND/OR RESISTANCE IS NOT FELT.

Storage: Store between 15°–30°C (59°–86°F).
KEEP OUT OF REACH OF CHILDREN.

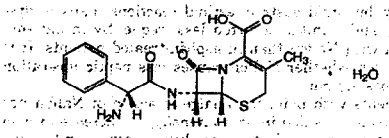
Caution: Federal law prohibits dispensing without prescription.

KEFLEX®

[kef 'leks]
(cephalexin)
USP

DESCRIPTION

Keflex® (Cephalexin, USP) is a semisynthetic cephalosporin antibiotic intended for oral administration. It is 7-(D-α-Amino-α-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid monohydrate. Cephalexin has the molecular formula $C_{16}H_{17}N_3O_4S \cdot H_2O$ and the molecular weight is 365.41. Cephalexin has the following structural formula:



The nucleus of cephalexin is related to that of other cephalosporin antibiotics. The compound is a zwitterion; ie, the molecule contains both a basic and an acidic group. The isoelectric point of cephalexin in water is approximately 4.5 to 5.

The crystalline form of cephalexin which is available is a monohydrate. It is a white crystalline solid having a bitter taste. Solubility in water is low at room temperature; 1 or 2 mg/mL may be dissolved readily, but higher concentrations are obtained with increasing difficulty.

The cephalosporins differ from penicillins in the structure of the bicyclic ring system. Cephalexin has a *D*-phenylglycyl group as substituent at the 7-amino position and an unsubstituted methyl group at the 3-position.

Each Pulvule® contains cephalexin monohydrate equivalent to 250 mg (720 µmol) or 500 mg (1,439 µmol) of cephalexin. The Pulvules also contain cellulose, D & C Yellow No. 10, F D & C Blue No. 1, F D & C Yellow No. 6, gelatin, magnesium stearate, silicone, titanium dioxide, and other inactive ingredients.

After mixing, each 5 mL of Keflex, for Oral Suspension, will contain cephalexin monohydrate equivalent to 125 mg (360 µmol) or 250 mg (720 µmol) of cephalexin. The suspensions also contain flavors, methylcellulose, silicone, sodium lauryl sulfate, and sucrose. The 125-mg suspension contains F D & C Red No. 40, and the 250-mg suspension contains F D & C Yellow No. 6.

CLINICAL PHARMACOLOGY

Human Pharmacology —Keflex is acid stable and may be given without regard to meals. It is rapidly absorbed after oral administration. Following doses of 250 mg, 500 mg, and 1 g, average peak serum levels of approximately 9, 18, and 32 µg/mL respectively were obtained at 1 hour. Measurable levels were present 6 hours after administration. Cephalexin is excreted in the urine by glomerular filtration and tubular secretion. Studies showed that over 90% of the drug was excreted unchanged in the urine within 8 hours. During this period, peak urine concentrations following the 250-mg, 500-mg, and l-g doses were approximately 1,000, 2,200, and 5,ooo µg/mL respectively.

Microbiology—In vitro tests demons&ate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cephalexin has been show" to be active against most strains of the following microorganisms both in *vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Aerobes, Gram-positive:
Staphylococcus aureus (including penicillinase-producing strains)
Staphylococcus epidermidis (penicillin-susceptible strains)
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobes, Gram-negative:
Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Moraxella (Branhamella) catarrhalis
Proteus mirabilis

Note—Methicillin-resistant staphylococci and most strains of enterococci (*Enterococcus faecalis* [formerly *Streptococcus faecalis*]) ire resistant to cephalosporins, including cephalexin. It is not active against most strains of *Enterobacter* spp, *Morganella morganii* and *Proteus vulgaris*. It has no activity against *Pseudomonas* spp or *Acinetobacter calcoaceticus*.

Susceptibility Tests —**Diffusion** techniques: Quantitative methods that require measurement of zone diameters provide reproducible' estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized p&edure[1] that has been recommended for use with disks to test the susceptibility of microorganisms to cephalexin uses the 30-µg cephalothin disk. Interpretation involves correlation of the diameter obtained in the disk test with the minimal inhibitory concentration (MIC) for cephalexin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30-µg cephalothin disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥18	(S) Susceptible
15–17	(I) Intermediate
≤14	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by usually achievable concentrations of the antimicrobial compound in blood. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable concentrations of the antimicrobial compound in the blood are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See CLINICAL PHARMACOLOGY section for information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

Standardized susceptibility test procedures require the "se of laboratory control microorganisms. The 30-µg cephalothin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	zone Diameter (mm)
E. coli ATCC 25922	15-21
S. aureus ATCC *25923*	2 9 - 3 7

Dilution techniques:

Quantitative methods that are used to determine MICs provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure uses a standardized dilution methods (broth, agar, microdilution) or equivalent with cephalothin powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (µg/mL)	Interpretation
≤8	(S) Susceptible
16	(I) Intermediate
≥32	(R) Resistant

Interpretation should be as stated above for results using diffusion techniques.

As with standard diffusion techniques, dilution methods re-"ire the "se of laboratory control microorganisms. Standard cephalothin powder should provide the following MIC alues:

Microorganism	MIC (µg/mL)
E. coli ATCC 25922	4-16
S. aureus ATCC 29213	0.12-0.5

INDICATIONS AND USAGE.

Keflex is indicated for the treatment of the follow& infections when caused by susceptible strains of the designated microorganisms:

Respiratory tract infections caused by *S. pneumoniae* and *S. pyogenes* (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Keflex is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of Keflex in the subsequent prevention of rheumatic fever are not available at present.)

Otitis media due to *S. pneumoniae. H. influenzae.* staphylococci, streptococci, and *M. catarrhalis*

Skin and skin structure infectious caused by staphylococci and/or streptococci

Bone infections caused by staphylococci and/or *P. mirabilis*

Genitourinary tract infections, including acute prostatitis, caused by *E. coli, P. mirabilis,* and *K pneumoniae*

Note —Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS

Keflex is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

BEFORE CEPHALEXIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to Keflex.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cephalexin, and **may range from mild to life threatening. Therefore,** it **is important** to **consider this diagnosis in patients** with **diarrhea subsequent to the administration of antibacterial agents.**

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

Usage in Pregnancy —Safety of this product for use during pregnancy has not been established.

PRECAUTIONS

General —Patients should be followed carefully so that any side effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to Keflex occurs, the drug should be discontinued and the patient treated with the usual agents (eg, epinephrine or other pressor amines, antihistamines, or corticosteroids).

Prolonged use of Keflex may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Keflex should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

As a result of administration of Keflex, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets.

As with other β-lactams, the renal excretion of cephalexin is inhibited by probenecid.

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy —Pregnancy Category B —The daily oral administration of cephalexin to rats in doses of 250 or 500 mg/kg prior to and during pregnancy, or to rats and mice during the period of organogenesis only, had no adverse effect on fertility, fetal viability, fetal weight, or litter size. Note that the safety of cephalexin during pregnancy in humans has not been established.

Cephalexin showed no enhanced toxicity in weanling and newborn rats as compared with adult animals. Nevertheless, because the studies in humans cannot rule out the possibility of harm, Keflex should be used during pregnancy only if clearly needed.

Nursing Mothers —The excretion of cephalexin in the milk increased up to 4 hours after a 500-mg dose; the drug reached a maximum level of 4 µg/mL, the" decreased gradually, and had disappeared 8 hours after administration. Caution should be exercised when Reflex is administered to a nursing woman.

ADVERSE REACTIONS

Gastrointestinal -Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea end vomiting have been reported rarely. The most frequent side effect has been diarrhea. It was very rarely severe enough to warrant cessation of therapy. Dyspepsia, gastritis, and abdominal pain have also occurred. As with

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This product information was prepared in **June 1999.** Current information on these and other products of Dista Products Company may he obtain&J by direct inquiry to Lilly Research Laboratories, Lilly, Corporate Center, Indianapolis, Indiana **46285, (800) 545-5979.**

some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.

Hypersensitivity —Allergic reactions in the form of rash, urticaria, angioedema, and, rarely, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis have been observed. These reactions usually subsided upon discontinuation of the drug. In some of these reactions, supportive therapy may be necessary. Anaphylaxis has also been reported.

Other reactions have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, arthralgia, arthritis, and joint disorder. Reversible interstitial nephritis has been reported rarely. Eosinophilia, neutropenia, thrombocytopenia, and slight elevations in AST and ALT have been reported.

OVERDOSAGE

Signs and Symptoms —Symptoms of oral overdose may include nausea, vomiting, epigastric distress, diarrhea, and hematuria. If other symptoms are present, it is probably secondary to an underlying disease state, an allergic reaction, or toxicity due to ingestion of a second medication.

Treatment —To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR).* In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

Unless 5 to 10 times the normal dose of cephalexin has been ingested, gastrointestinal decontamination should not be necessary.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of cephalexin; however, it would be extremely unlikely that one of these procedures would be indicated.

The oral median lethal dose of cephalexin in rats is >5,000 mg/kg.

DOSAGE AND ADMINISTRATION

Keflex is administered orally.

Adults —The adult dosage ranges from 1 to 4 g daily in divided doses. The usual adult dose is 250 mg every 6 hours. For the following infections, a dosage of 500 mg may be administered every 12 hours: streptococcal pharyngitis, skin and skin structure infections, and uncomplicated cystitis in patients over 15 years of age. Cystitis therapy should be continued for 7 to 14 days. For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of Keflex greater than 4 g are required, parenteral cephalosporins, in appropriate doses, should be considered.

Pediatric Patients —The usual recommended daily dosage for pediatric patients is 25 to 50 mg/kg in divided doses. For streptococcal pharyngitis in patients over 1 year of age and for skin and skin structure infections, the total daily dose may be divided and administered every 12 hours.

Keflex Suspension

Weight	125 mg/5 mL
10 kg (22 lb)	1/2 to 1 tsp q.i.d.
20 kg (44 lb)	1 to 2 tsp q.i.d.
40 kg (88 lb)	2 to 4 tap q.i.d
Weight	**250 mg/5 mL**
10 kg (22 lb)	1/4 to 1/2 tsp q.i.d.
20 kg (44 lb)	1/2 to 1 tap q.i.d.
40 kg (88 lb)	1 to 2 tsp q.i.d.

or

Weight	125 mg/5 mL
10 kg (22 lb)	1 to 2 tsp b.i.d.
20 kg (44 lb)	2 to 4 tsp b.i.d.
40 kg (88 lb)	4 to 8 tap b.i.d.
Weight	**250 mg/5 mL**
10 kg (22 lb)	1/2 to 1 tsp b.i.d.
20 kg (44 lb)	1 to 2 tsp b.i.d.
40 kg (88 lb),	2 to 4 tap b.i.d.

In severe infections, the dosage may be doubled.

In the therapy of otitis media, clinical studies have shown that a dosage of 75 to 100 mg/kg/day in 4 divided doses is required.

In the treatment of β-hemolytic streptococcal infections, a therapeutic dosage of Keflex should be administered for at least 10 days.

HOW SUPPLIED

Keflex® For Oral Suspension, (or cephalexin, USP), is available in:

The 125 mg per.5 mL oral suspension* is available as follows:

100-mL Bottles	NDC 0777-2321-48 (M-201)
200-mL Bottles	NDC 0777-2321-89 (M-201)

The 250 mg per 5 mL oral suspension* is available as follows:

100-mL Bottles	NDC 0777-2368-48 (M-202)
200-mL Bottles	NDC 0777-2368-89 (M-202)
ID†100	NDC 0777-2368-33 (M-202)

Keflex® Pulvules®, (or cephalexin, USP), are available in:

The 250 mg Pulvules are a white powder filled into size 2 Para-Posilok® Cap, (opaque white and opaque dark green) that are imprinted with "Dista" end identity code "H69" cm the green cap, and Keflex 250 on the white body in edible black ink. They are available as follows:

Bottles of 20	NDC 0777-0869-20 (PU402)
Bottles of 100	NDC 0777-0869-02 (PU402)

The 500 mg Pulvules are a white powder filled into an elongated, size 0 Para-Posilok Caps (opaque light green and opaque dark green) that are imprinted with "Dista" and identity code "H71" on the dark green cap, and Keflex 500 on the light green body in edible black ink. They are available as follows:

Bottles of 20	NDC 0777-0871-20 (PU403)
Bottles of 100	NDC 0777-0871-02 (PU403)

* After mixing, store in a refrigerator. May be kept for 14 days without significant loss of potency. Shake well before using. Keep tightly closed.

† Identi-Dose® (unit dose medication, Dista).

Store at controlled room temperature, 15° to 30°C (59° to 86°F).

REFERENCES

1. National Committee for Clinical Laboratory Standards: Performance standards for antimicrobial disk susceptibility tests—5th ed. Approved Standard NCCLS Document M2-A5, Vol 13, No 24, NCCLS, Villanova, PA, 1993.
2. National Committee for Clinical Laboratory Standards: Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically—3rd ed. Approved Standard NCCLS Document M7-A3, Vol 13, No 25, NCCLS, Villanova, PA, 1993.

Literature revised December 15, 1998.
PV 0360 DPP [121598]

NALFON®

℞

[năl 'fŏn]

(fenoprofen calcium)

USP

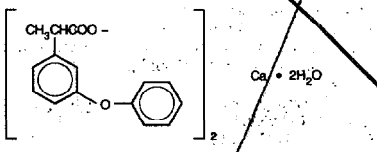
Capsules

DESCRIPTION

Nalfon® (Fenoprofen Calcium Capsules, USP) is a nonsteroidal, anti-inflammatory, antiarthritic drug. Nalfon capsules contain fenoprofen calcium as the dihydrate in an amount equivalent to 200 mg (0.826 mmol) or 300 mg (1.24 mmol) of fenoprofen. The capsules also contain cellulose, gelatin, iron oxides, silicone, titanium dioxide, and other inactive ingredients. The 300-mg capsules also contain D & C Yellow No. 10 and F D & C Yellow No. 6.

Chemically, Nalfon is an arylacetic acid derivative.

The structural formula is as follows:



Benzeneacetic acid, α-methyl-3-phenoxy-, calcium salt dihydrate, (±)-

Nalfon is a white crystalline powder that has the empirical formula $C_{30}H_{26}CaO_6 \cdot 2H_2O$ representing a molecular weight of 558.65. At 25°C, it dissolves to a 15 mg/mL solution in alcohol (95%). It is slightly soluble in water and insoluble in benzene.

The pKa of Nalfon is 4.5 @ 25°C.

CLINICAL PHARMACOLOGY

Nalfon is a nonsteroidal, anti-inflammatory, antiarthritic drug that also possesses analgesic and antipyretic activities. Its exact mode of action is unknown, but it is thought that prostaglandin synthetase inhibition is involved. Nalfon has been shown to inhibit prostaglandin synthetase isolated from bovine seminal vesicles. Reproduction studies in rats have shown Nalfon to be associated with prolonged labor and difficult parturition when given during late pregnancy. Evidence suggests that this may be due to decreased uterine contractility resulting from the inhibition of prostaglandin synthesis. Its action is not mediated through the adrenal gland.

Fenoprofen shows anti-inflammatory effects in rodents by inhibiting the development of redness and edema in acute inflammatory conditions and by reducing soft-tissue swelling and bone damage associated with chronic inflammation. It exhibits analgesic activity in rodents by inhibit&g the writhing response caused by the introduction of an irritant into the peritoneal cavities of mice and by elevating pain thresholds that are related to pressure in edematous hindpaws of rata. In rats made febrile by the subcutaneous administration of brewer's yeast, fenoprofen produces antipyretic action. These&i?& are characteristic of nonsteroidal, anti-inflammatory, antipyretic, analgesic drugs.

The results in humans confirmed the anti-inflammatory and analgesic actions found in animals. Tbe emergence and degree of erythemic response were measured in adult male volunteers exposed to ultraviolet irradiation. The effects of Nalfon, aspirin, and indomethacin were each compared with those of a placebo. AU 3 drugs demonstrated antierythemic activity.

In patients with rheumatoid arthritis, the anti-inflammatory action of Nalfon has been evidenced by relief of pain, increase in grip strength, and reductions in joint swelling, duration of morning stiffness, and disease activity (as assessed by both the investigator and the patient). The anti-inflammatory action of Nalfon has also been evidenced by increased mobility (ie, a decrease in the number of joints having limited motion).

The use of Nalfon in combination with gold salts or corticosteroids has been studied in patients with rheumatoid arthritis. The studies, however, were inadequate in demonstrating whether further improvement is obtained by adding Nalfon to maintenance therapy with gold salts or steroids. Whether or not Nalfon used in conjunction with partially effective doses of a corticosteroid has a "steroid-sparing" effect is unknown.

In patients with osteoarthritis, the anti-inflammatory and analgesic effects of Nalfon have been demonstrated by reduction in tenderness as a response to pressure and reductions in night pain, stiffness, swelling, and overall disease activity (as assessed by both the patient and the investigator). These effects have also been demonstrated by relief of pain with motion and at rest and increased range of motion in involved joints.

In patients with rheumatoid arthritis and osteoarthritis, clinical studies have shown Nalfon to be comparable to aspirin in controlling the aforementioned measures of disease activity, but mild gastrointestinal reactions (nausea, dyspepsia) and tinnitus occurred less frequently in patients treated with Nalfon than in aspirin-treated patients. It is not known whether Nalfon causes less peptic ulceration than does aspirin.

In patients with pain, the analgesic action of Nalfon has produced a reduction in pain intensity, an increase in pain *relief, improvement in total analgesia scores,* and a sustained analgesic effect.

Under fasting conditions, Nalfon is rapidly absorbed, and peak plasma levels of 50 μg/mL are achieved within 2 hours after oral administration of 600-mg doses. Good dose proportionality was observed between 200-mg and 600-mg doses in fasting male volunteers. The plasma half-life is approximately 3 hours. About 90% of a single oral dose is eliminated within 24 hours as fenoprofen glucuronide and 4'-hydroxyfenoprofen glucuronide, the major urinary metabolites of fenoprofen. Fenoprofen is highly bound (99%) to albumin.

The concomitant administration of antacid (containing both aluminum and magnesium hydroxide) does not interfere with absorption of Nalfon.

There is less suppression of collagen-induced platelet aggregation with single doses of Nalfon than there is with aspirin.

INDICATIONS AND USAGE

Nalfon is indicated for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis. It is recommended for the treatment of acute flare-ups and exacerbations and for the long-term management of these diseases.

Nalfon is also indicated for the relief of mild to moderate pain.

CONTRAINDICATIONS

Nalfon is contraindicated in patients who have shown hypersensitivity to it.

The drug should not be administered to patients with a history of significantly impaired renal function.

Nalfon should not be given to patients in whom aspirin and other nonsteroidal anti-inflammatory drugs induce the symptoms of asthma, rhinitis, or urticaria, because cross-sensitivity to these drugs occurs in a high proportion of such patients.

WARNINGS

Risk of GI Ulceration, Bleeding, and Perforation with NSAID Therapy —Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in, therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to 2 years duration, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc, no risk factors (eg, age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding